Summary Minutes of the Microbiology Devices Panel Meeting

May 20, 1999

Chairperson
Patricia Charache, M.D

Executive Secretary
Freddie M. Poole, M.T.

Members
Margaret R. Hammerschlag, M.D.
Natalie L. Sanders, M.D. M.P.H.
Carmelita U. Tuazon, M.D.
Melvin P. Weinstein, M.D.
Michael L. Wilson, M.D.

Temporary Voting Member
Paul H. Edelstein, M.D.

Industry Representative
David W. Gates, Ph.D.

Consumer Representative
Stanley M. Reynolds

Consultants
Richard O'Brien, M.D.
L. Barth Reller, M.D.
Steven C. Specter, M.D.

FDA Representatives

Division Director
Steven I. Gutman, M.D., M.B.A.

FDA Presenters
John Dawson
Roxanne G. Shively, M. S.
Patricia M. Simone, M.D.

Attendees
May 21, 1999

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Executive Secretary
Freddie M. Poole, M.T.

Members
Margaret R. Hammerschlag, M.D.
Natalie L. Sanders, M.D. M.P.H.
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Michael L. Wilson, M.D.

Industry Representative
David W. Gates, Ph.D.

Consumer Representative
Stanley M. Reynolds

Consultants
Adamadia Deforest, Ph.D.
L. Barth Reller, M.D.
Steven C. Specter, M.D.
John A. Stewart, M.D.
Robert N. Wolfson, Ph.D., M.D.

Guest
John F. Rodis, M.D.

FDA Representatives

Division Director
Steven I. Gutman, M.D., M.B.A.

FDA Presenters
Larry M. Anderson, M.D.
Thomas E. Simms

CALL TO ORDER

Dr. Charache called the meeting to order at 10:03 a.m. Following panel introductions, **Ms. Poole** read the conflict of interest statement. The agency determined that past interest in other firms with issues not related to today's discussion did not preclude full participation of **Drs. Edelstein, Hammerschlag, Weinstein,** and **Wilson. Dr. O'Brien** reported that his institution was involved in a related matter with the sponsor, but it would not preclude his participation in the discussion of *M. tuberculosis.* **Dr. Edelstein** was appointed temporary voting member for today's session.

OLD BUSINESS

Ms. Poole stated that the panel last convened on February 11-13, 1998, at which time the panel recommended that guidance documents be developed for the issues discussed. Ms. Poole reported that the agency was currently developing guidance documents as recommended.

NEW BUSINESS

Dr. Charache stated that the agenda item for the morning was a premarket notification submission for Digene Corporation's Hybrid Capture CMB Nucleic Acid Hybridization Assay for the Chemiluminescent Detection of Cytomegalovirus (CMV) DNA in white blood cells. The focus of the discussion was on the use of signal amplification terminology.

MANUFACTURER'S PRESENTATION

Mark A. Del Vecchio, Associate Director of Regulatory and Clinical Affairs at Digene Corporation, presented the basis for the amendment, to allow the use of signal amplification terminology, and described the product's review history. He noted that the term had been used to describe the technology in discussions with DCLD about other Digene products. The terminology was submitted in an approved PMA Supplement for the Hybrid Capture System HPV Test (P890064) in August 1997. However, DCLD determined that Digene could not use the term "signal amplification" in its labeling for the assay under discussion and instead proposed the term "signal enhancement" to describe the hybrid capture technology. Digene accepted this terminology to obtain clearance of their 5 10(k), but maintained that "signal enhancement" does not accurately or scientifically describe the technology and that the term "signal amplification" is applied to the technology in peer-reviewed literature and the scientific community.

James Lazar, Ph.D., Director of Clinical Sciences at Digene Corporation, provided the technical basis for describing hybrid capture as signal amplification. He cited FDA's *Review Criteria for Nucleic Acid Amplification-Based In Vitro Diagnostic Devices for the Detection of Infectious Microorganisms* and the definition of signal amplification by the NCCLS. He gave examples of peer-reviewed literature that describes hybrid capture as signal amplification and noted that FDA had not provided any literature references that refutes these descriptions.

Larry Krika, Ph.D., consultant to Digene, provided concepts for detection methodologies, including; ELISA, probe amplification, signal amplification via multiple labeling (1 and 2),and hybrid capture/branched DNA, and target amplification. He stated that detection systems can be categorized by: number of recognition events; number of labels per probe and number of signals generated from the label. He defined a signal amplification assay as "an assay format that incorporates multiple recognition events and multiple labels to increase the measured signal by orders of magnitude above a simple one-label, one-probe, one-binding event design."

Alison Cullen of Digene's Research & Development Dept., presented on the clinical performance of hybrid capture technology. The study she described compared three different methods: culture; (PCR); and Hybrid Capture Technology. **Ms. Cullen** stated that the studies demonstrated that hybrid capture (signal amplification) and Amplicor (PCR) (target amplification) had statistically equivalent clinical performance and that hybrid capture and Amplicor (PCR) were both significantly more sensitive than culture. She concluded that the Digene test is significantly more sensitive than tissue culture, traditional ELISA and direct probe tests. Hybrid capture shows equivalent clinical performance to the available target and probe amplification detection systems such as PCR and LCR.

Jonathan Kahn, Esq, Regulatory counsel to Digene, summarized the sponsor's position on use of 'signal amplification" terminology. He stated that the FDA has legitimate concerns about where to "draw the line" in terms of use of signal amplification, but Digene believes the "line" has been drawn improperly on the basis of science and peer-reviewed literature. The term signal amplification has become well recognized and use of a different term might prejudice potential users to believe that the Digene technology is a lesser technology. Of the four options proposed by the FDA, he stated that Digene finds option "c" acceptable; i.e., nucleic acid signal amplified solution hybridization assay.

Dr. Charache then invited the panel to ask questions of the sponsor. **Dr. Edelstein** asked what methods could be used to determine when the term is appropriate and whether quantifiable approaches and non-theoretical methods of determination are available. **Dr. Krika** replied that one could use a "one-label, one-probe" assay to begin to compare size or feature analysis could be used; e.g., multiple probe. **Dr. Charache** asked about the discrepancy between 3,284 amplification enhancement and 700 copies per milliliter used in the study. **Dr. Krika** replied that the two figures are not directly comparable as they did not represent signal generation but sensitivity detection figures.

FDA's PRESENTATION

Prasad Rao, Ph.D., Scientific Reviewer, presented the FDA's perspective on the use of "signal amplification" terminology. He noted that reimbursement coding is affected by terminology, although FDA decisions are to be independent of those concerns. He commented that if the hybrid capture system is described as a signal amplification test,

many ELISA tests might also qualify for the classification although those assays are not designated signal amplification reactions. Signal amplification technologies originated in nucleic acid detection as alternatives to target amplification. The branched DNA (bDNA) assay is generally accepted as a signal amplification reaction and consists of compound probes that have complimentarity to the target and extenders that bind to amplification multimers. In comparison, the Hybrid Capture System is a direct probe detection method where the primary signal is detected by enzyme conjugated antibodies. This situation is similar to biotinylated probe detection methods or other ELISA systems.

Dr. Rao stated in conclusion that the issues raised with the use of "signal amplification" terminology were: (1) Is the detection method used here similar or unique when compared to other ELISA assays for antigen detection or biotinylated probe detection methods? (2) Is there multiplication of replication of initial signal achieved in the Digene Hybrid Capture System@ which is expected in a true signal amplification reaction?

Dr. Charache then invited the panel to ask questions of the FDA presenter. The sponsor requested and was granted five minutes to respond to the FDA's presentation.

OPEN PUBLIC HEARING

Dr. Charache opened the meeting for public discussion. There was no response from the public.

OPEN COMMITTEE DISCUSSION AND RECOMMENDATIONS

Dr. Charache opened the discussion. The panel agreed to focus the discussion on FDA's questions, The panel agreed that in answer to question 1, the detection method used in the CMV assay was unique

Question#2: Given the nature of the technology in this device and the performance likely to be seen by the use of this test, which of the following is an appropriate description of the Digene Hybrid Capture System@ assay: (a) nucleic acid solution hybridization assay. (b) Nucleic acid signal enhanced solution hybridization assay. (c) Nucleic acid signal amplified solution hybridization assay. (d) other recommended nomenclature.

Dr. Charache asked the panel for comments on FDA's question. **Dr. Specter** said that options a, b, and c were all acceptable and that enhancement and amplification are synonymous terms. Safety and efficacy would not be compromised by the terminology. Labeling is a laboratory issue. **Dr. Hammerschlag** pointed out that the performance of signal amplification assays using nucleic acid ELISA tests are very different in performance by the ability to detect organisms. These tests should be judged on performance. **Dr. Gates** stated that the term "signal amplification" is not an implied claim or inferred claim, nor does it really tell how the test performs, **Dr. Charache** asked what would prevent a manufacturer of an ELISA test from insisting on a label of signal amplification. Are there legal issues? **Dr. Gutman,** the FDA representative,

replied that FDA has authority to prevent such usage. The agency does not consider enhancement and amplification as synonymous terms. **Dr. Sanders** asked how much amplification is required to merit the use of the term. **Dr. Reller** noted that options b and c are somewhat ambiguous and suggested the term "nucleic acid hybridization with signal amplification". **Dr. Tuazon** said that the performance and diagnostic utility matter more to the clinician. **Dr. Edelstein** replied that the use of the term has marketing and reimbursement implications.

Dr. Charache then polled the committee. Members.unanimously rejected option a. **Dr. Weinstein** indicated mixed feelings about option b, but other members responded negatively. With the exception of **Dr. Edelstein,** all members rejected option c. The panel was presented with two choices for option d: (1) signal amplified nucleic acid hybridization assay and (2) nucleic assay hybridization assay with signal amplification. The panel recommended that either of the choices were acceptable.

Dr. Gutman asked committee members for further guidance on how to determine the point at which the term signal amplification can be applied. **Dr. Reller** suggested performance of the assays and **Dr. Weinstein** suggested a differentiation based on the magnitude of copies.

The meeting recessed at 12:30 p.m.

CALL TO ORDER

Dr. Charache reconvened the meeting at 1:37 p.m. The afternoon agenda item was a premarket approval application supplement to modify the device indications to include AFB smear negative respiratory specimens for the diagnosis of active pulmonary tuberculosis disease on the Gen-Probe Amplified Mycobacterium Tuberculosis Direct (MTD) Test. MTD is a target-amplified nucleic acid probe test used for detection of Mycobacterium tuberculosis complex in sediments prepared from sputum (induced or expectorated), bronchial specimens, or tracheal aspirates from patients with smear positive respiratory specimens.

MANUFACTURER'S PRESENTATION

Glen Frieberg, Sr. Director, Regulatory Affairs, Gen-Probe Corporation, introduced Gen-Probe presenters and other personnel present, and explained the device modifications in the PMA supplement.

Vivian Jonas, Product Development Manager, Gen-Probe Corporation, presented the differences between MTD and enhanced MTD; MTD performance since the enhanced MTD launch and the package insert. She stated that their data show that MTD is a robust assay with no observed performance issues. Some customers have validated MTD according to CLIA for use with smear negative samples. MTD has been available in Europe (1992) and Japan (1994) with no smear restrictions. She described the current warnings and interpretation of results in the package insert and concluded that the

addition of clinical data with respect to smear negative information is all that is required for the application,

Katie Smith, Ph.D., Director, Clinical Affairs, Gen-Probe Corporation, presented an overview of AFB smear and culture for TB and described the clinical trials, conducted at 7 geographically diverse sites. Unlike prior studies, clinical physician diagnosis of TB was used as an endpoint. The subjects had presented with clinical suspicion of TB and were not on therapy. An expert panel process was used to standardize the diagnosis of TB. Since some MTD data were generated from frozen specimens, statistical analyses were conducted to determine whether the fresh and frozen data could be pooled.

Antonino Catanzaro, M.D., medical consultant for Gen-Probe, presented the clinical diagnosis of tuberculosis. He noted that MTD, outperformed three other tests: clinical exam, CXR, and AFB and is comparable to culture which has a recognized sensitivity of 80-90%. On specificity, he found that MTD outperformed clinical exam and CXR. He cited benefits for use of MTD with patients who do not have TB; i.e., avoiding unnecessary contact evaluations and unnecessary exposure to anti-TB medications. Benefits for patients who do have TB include the ability to start effective therapy earlier and avoid potential transmission of TB. He noted the difficulty of defining "suspicion" of TB.

Dr. Charache then invited the panel to question the sponsor, **Dr. O'Brien** suggested that the number of patients presumptively treated based on a high index of clinical suspicion would be useful for supporting the applicant's position that the MTD test would allow more efficient diagnosis and treatment. **Dr. Edelstein** asked how frozen specimens were stored. **Dr. Jonas** answered the question. **Dr. Weinstein** asked about the role of prevalence in determining positive predictive value as predictive values are affected by low prevalence. The data appear to show that one in three is a false positive. Without guidance in the package insert on prevalence, one out of three patients could be' treated incorrectly.

FDA's PRESENTATIONS

Patricia M. Simone, M.D., Medical Officer, CDC, discussed the impact of NAA on TB treatment and control programs. Problems of inaccurate test results include unnecessary treatment and contact investigations and delay in therapy. She noted the decreased federal funding for TB and the necessity for careful allocation of resources.

Roxanne Shively, Lead Scientific Reviewer, Microbiology Branch, described the clinical trial and outlined FDA concerns. The test could be used with any specimen from an untreated patient and the applicant believes that interpretation should be the same for smear positive and negative specimens. Patients are described as TB suspects, which may be an inadequate definition of the study patient population. **Ms. Shively** questioned whether conclusions from an evaluation with such patients would apply to a selected

population or to a broad spectrum of patients. She explained different approaches for representing MTD performance using the combined fresh and frozen MTD data. She commented that prevalence would be very low in most settings without using selection criteria.

John Dawson, Mathematical Statistician, Office of Surveillance & Biometrics, presented statistical issues, and discussed the poolability issues both for combining MTD data from different clinical sites and for combining MTD data from testing fresh and frozen specimens. He reiterated the use of the 1st specimen analysis as being an approach that maximizes the number of patients and avoids the problems of bias effects from multiple patients sampling. He also indicated that it would be ideal to incorporate results of additional MTD testing into any analysis despite the inherent flaws in the study design. **Dr. Charache** then provided the sponsor the opportunity to present additional information. **Dr. Smith** presented an analysis of their data to demonstrate that the data collected from fresh and frozen specimens could be pooled.

OPEN PUBLIC HEARING

Dr. Charache opened the meeting for public discussion. There were no comments from the public.

OPEN COMMITTEE DISCUSSION AND RECOMMENDATIONS

Dr. Charache opened the discussion by asking the Primary Reviewer, **Dr. Wilson,** to provide his analysis of the data. **Dr. Wilson** commented that he had concerns with (a) the low number (27) of patients that had smear negative TB that were included in the study, (b) the use of patient diagnosis as the gold standard when there were no standardized criteria for diagnosis, and (c) the determination of prevalence. **Dr. Gates,** the Industry Representative responded that the Panel should not be concerned with the numbers since FDA's statistician was not concerned. **Dr. O'Brien,** the CDC consultant to the Panel, added that the use of clinical diagnosis is important in drug studies. The panel then agreed to proceed by discussing the FDA questions.

Question #1: The applicant proposes to pool MTD data from retesting frozen lysates (done at a single separate laboratory facility) with MTD data from testing "fresh" specimens at 6 of 7 clinical laboratories. Can this pooled data be used to characterize performance for individual sites? a. If yes, how should this data be represented in the labeling? b. Is the data (fresh, frozen, or pooled) adequate to characterize individual site performance for the use of this device? c. If not, what types of data or further analysis should be used for laboratory/site performance evaluation?

After discussing the issues surrounding pooling of data, **Dr. Charache** polled the panel to determine if they believed that pooled data could be used to characterize performance for individual sites. Responses were **Hammerschlag: No,** the sites were too varied.

Sanders: No. Weinstein: No comment. **Reynolds: No. Gates Yes. Reller: No. Specter:** No comment. **O'Brien: Yes. Edelstein: No. Wilson: No.**

The Panel then discussed how the data should be presented in the labeling. **Dr. O'Brien** commented on the difficulty of obtaining adequate numbers of patients with the characteristics necessary for testing. **Dr. Edelstein** stated that fresh and frozen data should be separated and sensitivities reported for each group, and confidence levels (CIs) should be included in the label for different population prevalence.

As to the adequacy of the data, **Dr. Hammerschlag** commented that the heterogeneous nature of the sites made it difficult to extrapolate data on performance. **Dr. Specter** asked for information about the fresh smear negative specimens; i.e., how many went to panel and what were their characteristics and disposition. **Dr. O'Brien** said that data from other studies, such as the Galveston study, had relevant data for determining performance.

Question #2: Should the instructions for use in labeling include information to clarify differences in expected performance for smear negative versus smear positive specimens? a. If so, where and how is this information best communicated? b. If not, are any other guidance or caveats in the labeling appropriate to ensure safe and effective use of the MTD with smear negative specimens?

Dr. Charache asked what population would be used to determine predictive value. **Dr. Edelstein** said that different criteria were needed for smear negative and smear positive populations, therefore instructions should be provided in the insert for interpretive criteria, and the clinician must estimate pre-test probability. **Dr. Charache** commented on the high number of false positives non-TB cases that were isolated at Johns Hopkins and without good clinical guidelines, this number could pose problems for an institution. **Dr. Hammerschlag** said that instructions should contain a qualification that there is a probability that a false positive is possible, and that results should be considered in terms of the population. **Dr. Gates** responded that laboratory personnel usually know the impact of prevalence on test results. **Dr. Weinstein** replied that the package insert should include a graph similar to the one designated B-l in book 3.

Dr. Charache asked the panel if they could determine a percentage of false positives that would mean an institution should not perform the test. **Dr. Hammerschlag** said that such a recommendation should come from the CDC.

Dr. Reller said the issue is whether testing should be performed on smear negative specimens. Of the fresh specimens presented in the study, 17 cases were smear negative. He asked how many of these were culture positive? He said that the package insert should contain language about issue prevalence and the test's performance on culture-positive, smear-negative patients.

Dr. Charache asked whether a patient should be treated who has a positive MTD and negative smear. **Dr. Reller** said that culture testing is necessary in both instances. **Dr. Specter** said that both a culture and clinical diagnosis are necessary.

Dr. Charache asked for a recommendation about repeat testing of smear negative specimens. **Dr. Edelstein** said that information on the clinical suspicion of the disease would be required to determine if test results should be repeated. **Dr. Reller** said that a positive MTD test needs a culture confirmation and susceptibility testing. **Dr. Tuazon** responded that instructions should clarify the differences in expected performance for smear negative specimens. **Dr. O'Brien** did not believe there were sufficient data to provide a recommendation.

Dr. Charache summarized the suggestions made about what should be presented; i.e., information relevant to difference in results, relationship of predictive value to prevalence and requirement for a culture to confirm MTD positive results. She asked for recommendations on the language for the requirement for a-culture. **Dr. Hammerschlag** agreed with the suggestions and addition of a graph. **Dr. Sanders** agreed that culture must be done and the addition of a prevalence table. **Drs. Weinstein, Specter, Tuazon, Wilson** and **Mr. Reynolds** concurred, **Dr. Gates** agreed that a graph be added but the language should not be as strong and recommended "should". **Dr. Reller** did not comment. **Dr. O'Brien** recommended including a warning that the positive predictive value for smear negatives was based on 11 percent prevalence. The positive predictive value is likely to be much lower with other populations. **Dr. Edelstein** recommended "should" and a warning concerning the impact of prevalence on results.

Dr. Charache asked whether the prevalence results in the clinical trial should be included in the package insert. Several panelists agreed that information must be provided about the relationship between the impact of prevalence on positive predictive value. **Dr. Edelstein** proposed adding 95% confidence intervals for those estimates. **Dr. Reller** added that the package insert should also contain instructions to clarify that expected positive and predictive values varies with prevalence or the pretest probabilities.

Dr. Gutman asked for clarification on the panel's recommendations concerning the idea of differential labeling for the two subsets of data. **Dr. Charache** rephrased the question. Should there be separate tables and recommendations for interpretation for the smear positive and smear negative. **Drs. Hammerschlag, Weinstein, Specter, O'Brien, Edelstein, Tuazon, Wilson,** and **Mr. Reynolds** answered yes.

Question #3: Does the current study (plus data and information from previous studies) provide sufficient evidence to modify current labeling as requested by the applicant? a. If yes, does the panel have recommendations for other labeling modifications (e.g. contraindications, warnings or limitations) to ensure safe and effective use for the requested change to the intended use? (1) Should MTD testing of smear negative specimens by indicated for selected patients (those with a high clinical suspicion)? (2) Should labeling explicitly link use of the MTD to testing smear negative patients in high prevalence settings? b. If no, what additional data

or data analyses might be appropriate to support the requested intended use modification? Are there other alternatives such as labeling modifications that could support MTD use for smear negative patients?

All panel members answered yes with the exception of **Drs. Reller, O'Brien** and **Wilson. Dr. Wilson** explained that there were only **17** smear negative patients, not enough data he believes to modify the labeling.

Dr. Charache then asked the panel to consider item 1 under A. Should MTD testing of smear-negative specimens be indicated in selected patients; i.e., those with a high clinical suspicion or should it be open to anyone who gets a culture? **Dr. Hammerschlag** indicated that the previous limitations are sufficient. **Dr. Sanders** suggested a global use in either smear positive or negative. **Drs. Weinstein, O'Brien, Edelstein,** and **Tuazon,** and **Mr. Reynolds** answered yes. **Dr. Gates, Specter** and **Edelstein** answered no.

VOTE AND RECOMMENDATIONS

The Executive Secretary identified the voting members. **Dr. Wilson** moved that the PMA supplement be approved with conditions discussed by the panel. **Dr. Hammerschlag** seconded the motion. The conditions were: (1) A graph showing prevalence effects on positive predictive values and guidance for interpreting be included in the package insert. (2) A warning statement to indicate that study data were based on a population with a prevalence of 11%. (3) Positive MTD results for smear negative patients must be confirmed by culture. (4) Separate performance representations for smear negative and smear positive patients. (5) Ninety-five percent confidence bands be included in the analysis of predictive value. (6) Post-approval studies should be conducted to assess the prevalence effects on test performance. And (7) Interpretation of MTD results for smear negative patients should consider pretest probabilities.

The panel voted unanimously for approval with conditions.

The meeting was adjourned at 7:30 p.m.

CALL TO ORDER

Dr. Charache called the meeting to order at 9:50 a.m. The panel members were introduced.

NEW BUSINESS

Thomas B. Shope, Jr., Ph.D., Special Assistant to the Director, Office of Science and Technology, Center for Devices and Radiological Health (CDRH) reported on the impact of the Year 2K data problem on medical devices.

Larry G. Kessler, SCD, Director, Office of Surveillance & Biometrics, CDRH, reported on post-market evaluation at CDRH. He explained that under the Medical Device Reporting Program (MDR), manufacturers must report deaths, serious injuries and malfunctions to FDA if a medical device might have caused the event. He cautioned the panel that when considering postmarket studies, they should clearly specify the public health question to be addressed and provide a clear understanding of how data can be used.

Dr. Sanders asked Dr. **Kessler** to explain international harmonization. **Dr. Kessler** explained the work of the Global Harmonization Task Force, which promotes worldwide consistency in regulations and ensures that information about problems with medical devices is rapidly communicated.

Dr. Gutman then presented a Certificate of Appreciation signed by the new FDA Commissioner, Jane Henney, M.D. to **Dr. Specter** for completion of his term as a Voting member of the panel.

Mrs. Poole then read the conflict of interest statement. No conflicts were reported.

Dr. Charache stated that the agenda included two premarket approval applications. (1) Biotrin International, Ltd. Parvovirus B 19 IgG enzyme immunoassay (EIA) indicated for use in all women where there is a suspicion of exposure to Parvovirus B19 as a marker of previous infection. (2) Biotrin Parvovirus B 19 IgM EIA indicated for use in conjunction with the Parvovirus B 19 IgG EIA assay for the testing of pregnant women who have sonographic evidence of abnormal fetal development such as hydrops fetalis, and to determine immunological status during the first trimester of pregnancy.

MANUFACTURER'S PRESENTATION

Cormac Kilty, Ph.D., Managing Director of Biotrin International, Ltd. (Biotrin), introduced the Biotrin presenters and staff present. **Sean Doyle, Ph.D.,** Consultant for Biotrin, described Parvovirus B 19 and the technical development of Biotrin's Parvovirus B 19 IgM and IgG EIA assays. He presented proposed language for the revised indications for use and the cut-off determination of the assays.

Jeanne Jordan, Ph.D., consultant for Biotrin described the clinical data from the three studies: Magee Women's Research Institute (MWRI) study; CDC Characterized Panel; and a second

MWRI study in which characterized sera from CDC were analyzed by IFAA and compared to the CDC results. She concluded that the studies demonstrated that the IgG and IgM assays provide accurate serologic status determination and identified patients with presumptive risk of fetal infection.

Mary E. D'Alton, M.D., consultant for Biotrin described the clinical utility of accurate tests for Parvovirus and the problems resulting from non-standardized tests. Patients not at risk can be identified. Invasive testing can be avoided. Lifesaving therapy can be initiated.
Cormac Kilty, Ph.D., summarized the sponsor's presentation. He stated that Biotrin believes that they have a reproducible test that has been used in Europe for five years. The devices have a validated cut-off. The test shows low cross-reactivity and very specific immunological class detection capability. It is more specific and sensitive than what is available for research purposes. The test shows a high degree of agreement with three different assays: the CDC assay, an assay using a different coated protein of the virus and an assay using a different detection method in immunofluorescence. The test can provide accurate information for the assessment of fetal risk, which will obviate the need for unnecessary testing.

Dr. Charache invited the panel to ask questions of the sponsor. **Dr. Specter** asked whether there is clinical significance in figures presented relative to seropositivity in the pregnant women survey. **Dr. Doyle** replied that the subjects were women of childbearing age with no indication of clinical disease. **Dr. Hammerschlag** stated that the prevalence data for antibody positivity in selected exposed population vs. a general population was important. **Dr. Wolfson** asked which of the three data sets is the reigning gold standard. **Dr. Doyle** replied that he believes the enzyme immunoassays are the gold standard because the antigens are in conformationally intact structure and are the most validated. **Dr. Charache** asked for an explanation of the variability of the IgM in the reproducibility studies. **Dr. Doyle** provided an explanation.

Dr. Charache asked how the test would be used with high-risk job categories. **Dr. D 'Alton** replied that if the IgG assay is positive, a woman can be certain of no fetal risk upon exposure to a child with fifth disease. **Dr. Sanders** asked for an estimate of the number of babies with fetal hydrops anemia who might be saved if a laboratory diagnosis is made. **Dr. D'Alton** replied the range usually quoted is between 2.5% and 9%. If the disease can be identified early, about 80% of the patients with Parvovirus can be treated.

FDA'S PRESENTATION

Thomas E. Simms, the Lead Reviewer, presented FDA's analysis of the clinical data and commented on the problems posed by assay to assay comparison. The review team established a testing algorithm to evaluate single point patient specimens. This involved splitting the Magee study population into three subgroups: acute recent infection, previously infected and not previously infected and showed the agreement between the serological diagnosis using the reference method to the Biotrin results. There was agreement of 78.9% for the acute recent; 97.3% for the previously infected and 100% for the not previously infected. He presented the calculated predictive values for each subgroup. **Mr. Simms** also discussed the analysis of two subgroups, pregnant women and children, in the CDC characterized panel. He outlined FDA's concerns and questions and said that both the Magee and CDC studies suggest the advisability of

a recommendation that both assays be used, even if testing a patient to determine previous infection or exposure.

In response to questions from **Dr. Charache** on previous infection vs. immune status, **Dr. Kilty** and **Mr. Simms** agreed that the IgG assay couldn't be used to guarantee immunity.

Larry M. Anderson, M.D., Panel Discussant and Chief, Respiratory and Enteric Viruses Branch, National Center for Infectious Disease, CDC, gave an overview of the clinical characteristics of Patvovirus B 19 and provided a background on the epidemiology of infection and some perspectives on diagnosis of B 19. The panel then questioned Dr. Anderson on assay sensitivity, cross-reactivity with other viruses, and interpretation of results for the B 19 IgG and IgM.

OPEN PUBLIC HEARING

Dr. Charache opened the meeting for public discussion. There was no response from the public.

OPEN COMMITTEE DISCUSSION

Dr. Charache opened the discussion and commented on the study design of the application. She commented that this would be the first FDA-approved assay, so it could become a benchmark for all other B19 assays. **Dr. Specter,** one of the primary reviewers, commented that some relevant clinical information was not evident for the patients in the CDC study and the Magee study. **Dr. Wolfson,** the other primary reviewer, was also concerned that approval of the assay might indicate establishment of a gold standard and about the inability of the test to identify a specific number of IgM positive individuals. He noted that the assay should be evaluated in the context of clinical presentation of the patients.

Dr. Charache asked the panel to focus their discussion on the FDA's questions.

Question #1:. Which data analysis is appropriate for these devices and claims? Assay-to-assay comparison, or comparison to the serologkal diagnosis?

Dr. Weinstein commented that in the absence of a gold standard for the assay, the comparison to serological diagnosis is preferable. **Dr. Wolfson** commented on the clinician's role in diagnosing patients used in Biotrin's tests and expressed concern about confusion between tests the CDC standard and tests compared to other serological methodologies. **Dr. Reller** commented that the comparisons to serological diagnosis and CDC standards are complimentary and suggested that the panel consider options a and b as one option, rather than considering them as being mutually exclusive.

Dr. Charache asked the panel to provide recommendations on question 1. The options were redefined as follows: (A) CDC data set and (B) pooled serological diagnostic data. After further discussion, the options were again redefined as (A) assay to assay and (B) serological diagnosis, defined as the consensus of multiple assays and IgG for the interpretation of the category of

previous infection. (C) CDC data, if available. The question was further defined to include 2 options for (C); (1) all CDC data (2) only CDC data for pregnant women.

The panel unanimously agreed on Option b . Option **c-l** was accepted, with the exception of one member for c-2.

Question #2: Do the results from the CDC serology panel allow expansion of the assay's indications for use; e.g. for the serological diagnosis of fifth disease in an adolescent population or serological diagnosis of Parvovirus B19 infection regardless of patient population?

Dr. Stewart commented that there were a very large number of B 19 positive children in the CDC data set **Dr. Hammerschlag** stated that the data could only support use with children with rash because no other information was available. She added that the data would be insufficient to extrapolate use with children with other hemoglobinapathies. **Dr. Reller** believed the assay should be intended simply to assess pregnant women.

The panel agreed that the results of the CDC serology panel could allow expansion of the assay's indications for use to the serological diagnosis of Fifth disease in an adolescent population.

Question #3: What would be the appropriate intended/indications for use for these assays? For example, are the following appropriate or should they be modified? Biotrin Parvovirus B19 IgG Assay - The Parvovirus B19 IgG Enzyme Immunoassay is intended for the qualitative detection of IgG antibodies to Parvovirus B19 in human serum and plasma. The test in conjunction with the Parvovirus B19 IgM EIA may be used in women of childbearing age where there is a suspicion of exposure to or infection with Parvovirus B19 as a marker of previous infection. *The use of this assay has not been established for diagnosing other Parvovirus associated diseases.*

Biotrin Parvovirus B19 IgM Assay - The Parvovirus B19 IgM Enzyme Immunoassay is intended for the qualitative detection of IgM antibodies to Parvovirus B19 in human serum of plasma. The test, in conjunction with the Parvovirus B19 IgG EIA, may be used in women of childbearing age where there is a suspicion of exposure to or infection with Parvovirus B19 to determine the women's serological status. The results of this assay may be used to make a serological diagnosis of acute or recent infection with Parvovirus B19. When testing pregnant women reactive IgM results should be considered presumptive when assessing fetal risk for Parvovirus B19 infection. *The use of this assay has not been established for diagnosing other Parvovirus associated diseases.*

Dr. Hammerschlag suggested that the statement include a modification that efficacy of the assay was not established with infections immunocompromised patients or patients with hemoglobinapathies. **Dr. Wolfson** suggested that risk should also be included, e.g. "women at risk" or "suspicion of exposure".

The panel unanimously agreed with the proposed language in question 3, with the provision that the statements for IgG and IgM be consistent.

Question #4. What are the appropriate result interpretations for the Biotrin assays? For example, for the pregnant woman or women of childbearing age population are the following appropriate or should they be revised?

Parvovirus B 19	Parvovirus B19	Interpretation
IgM Positive	IgG Positive	Presumptive Current/Recent Infection Fetus may be at risk
IgM Positive	IgG Negative	Presumptive Current/Recent Infection Fetus may be at risk
IgM Negative	IgG Positive	Infers past exposure/ infection. Minimal risk of Parvovirus B 19 infection to the fetus
IgM Negative	IgG Negative	Patient may be susceptible to Infection

All patients with repeatedly equivocal assay results should be redrawn within 1-2 weeks and assays repeated.

Dr. Specter suggested that the order of the table be changed so that IgM positive/IgG negative is first, that a comment be added about the potential for interpretation of cross-reactivity with EBV **Dr. Hammerschlag** suggested adding confidence intervals with the sensitivity calculations.

After a discussion on the chronological order of the interpretation of results, Dr. **Charache** asked for a consensus. The panel suggested that the four section boxes be ordered in the manner in which testing is usually done. The panel then discussed the interpretation for IgM positive IgG negative results. **Dr. Specter** recommended that an alert be added that interpretation must be made in light of the clinical situation. **Dr. Sanders** commented that the language used in the interpretation column and the analysis of data described in the package insert should be consistent.

The panel further discussed changes to the interpretation of results such as; the word "infers" to "implies", eliminating the word exposure, adding a warning that an IgG positive result can indicate recent infection and should be considered in the clinical context.

Question #5: From data previously submitted, both assays have been shown to produce false positive results when the patient is acutely infected or undergoing a reactivated infection with Epstein-Barr virus. What safeguards, if any, are necessary to alert the user of possible false positive assay results, e.g., labeling warnings and precautions?

For IgM Positive and/or IgG Positive results, should it be reported that this assay has demonstrated false positivity when the patient is undergoing an acute or reactivated Epstein-Barr virus infection? In addition, is it advisable to monitor the patient for Epstein-Barr virus infection, either acute or reactivated?

The panel agreed that a warning statement about false positive results obtained from patients with acute EBV infections is unnecessary. The limitation statements in the package insert should be sufficient.

Question #6. In 1997, the FDA issued a Public Health Advisory related to anti-Toxoplasma gondii testing. Should a similar health advisory be considered for these assays? # Assays are presumptive for the diagnosis of infection. #Serological diagnosis of infection should be confirmed. # Proper interpretation of assay results. For example, inform the physician that when a patient is presenting during an acute or recent infection both IgG and IgM will be present. Both the IgG and IgM assays should be ordered not just the IgM.

The panel agreed that a Public Health Advisory was unnecessary because the test was not yet on the market, and it was not known how it would be used and if that use would necessitate a public health advisory would be needed.
Dr. Charache then opened the meeting for comment from the Public. There being none, she invited the Industry to comment. They had no comments.

VOTE AND RECOMMENDATIONS

After the Executive Secretary read the conditions for approval or nor approval for a PMA, and identified the voting members, **Dr. Specter** motioned that the PMA be approved with conditions. **Dr. Sanders** seconded the motion. Some of the conditions were: 1) that the intended use statement be expanded to include for use with Fifth Disease and CDC data be included, 2) that the interpretation of results be modified to include a warning of interpretation with clinical symptoms, 3) that confidence intervals be reported with sensitivity data, and 4) that appropriate limitation statements be included.

The panel voted unanimously Approval with Conditions for the Biotrin Parvovirus B19 IgG PMA and the Biotrin Parvovirus B19 IgM PMA

Dr. Charache adjourned the meeting at 3:45 p.m.

I certify that I attended the meeting of the Microbiology Devices Panel on May 20-21, 1999, and that this summary accurately reflects what transpired.

Freddie Mae M. Poole, M.T.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Patricia Charache, M.D.
Chairperson

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